Breast Cancer in the 20th Century: Quest for the Ideal Therapy

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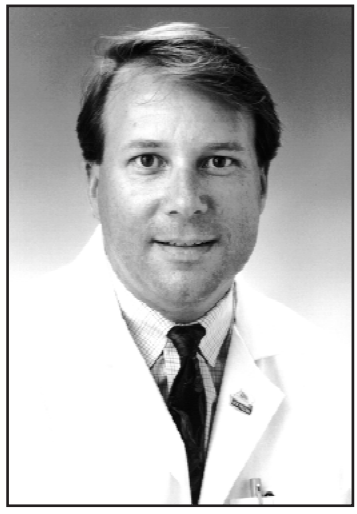

Dr. Borgen completed his General Surgery residency at Ochsner in 1989.

Introduction

The prospect of a new millennium provides an excellent opportunity for physicians, researchers, and the general public to look back at the last century and put our current understanding of breast cancer and other significant health threats into perspective. For breast cancer in particular, the 20th century was characterized by several paradigmatic changes in approach and witnessed a struggle to achieve the ideal therapy–one that represented the best compromise between treatments that were unnecessarily mutilating and those that were dangerously inadequate, a search that necessarily included modalities designed to enhance or replace surgery.

It became evident that breast cancer can be either a local or a systemic disease, ushering in the era of multimodal therapy integrating surgery, chemotherapy, hormonal therapy, and radiation therapy. (One of the earliest proponents of a multidisciplinary approach to the disease was Dr. Albert Segaloff from the Ochsner Clinic [1].) Early diagnosis proved to be essential in increasing the chances of survival and, with the development of radiologic technologies, mammography was shown to be the cornerstone of early detection. Improvements in radiology have produced a new class of devices capable of diagnosing and even treating nonpalpable breast cancers. Stereotactic biopsies are now commonly performed in the United States and, when benign, save a significant number of patients from undergoing unnecessary surgery.

For the majority of the 20th century, we relied upon a purely *descriptive* understanding of breast cancer derived from clinical observations. Late in the century, driven by the marriage of biochemistry and high technology, the new field of molecular biology began providing insights into the primal causes of breast cancer and confirmed that genetic aberrations lie at the core of all breast cancers. Researchers began to explore the genes responsible for tumor formation (oncogenes) and those genes responsible for protecting us against tumor formation (tumor suppressor genes). Much was learned about the cell to cell interactions that occur within a breast cancer and its environs (cell adhesion molecules) as well as the need for blood vessel development (angiogenesis) required by a tumor. It became very clear that breast cancer is not a single disease entity but rather a large family of diseases.

The age of genetic susceptibility testing began in the 1990s with the discovery of the *BRCA1* and *BRCA2* genes, which allow for the identification of a subset of patients at greatly increased risk of breast and other cancers. Although these tumor suppressor genes describe only a small fraction of breast cancers, they hold great promise for revealing fundamental biologic events in the evolution of breast cancers in general, partly because they are recessive at the cellular level.

Currently, a growing wealth of information suggests that a family of drugs–the selective estrogen receptor modulators (SERMs)–are capable of reducing the risk of breast cancer in selected individuals at high risk. The ultimate goal–the primary prevention of breast cancer–remains an ideal, but these discoveries move us closer to a *functional* understanding of the disease.

Surgery

As the 20th century dawned in America, the causes for breast diseases were poorly understood. Debate had raged throughout the previous century concerning the possibility that breast cancer was an infectious disease whose spread was hastened by surgery, an idea espoused by one of the preeminent surgeons of the day, James Syme (1799-1870) from Edinburgh. Syme's experience led him to believe that surgery should not be attempted for breast cancer because the result was almost uniformly unfavorable (2). Dr. John Brown, Syme's third surgical apprentice, published a moving description of the horrors of a mastectomy performed in the pre-anesthesia, pre-sterile technique era. His account, Rab and His Friends, provides insight into why virtually all patients died after surgery: sepsis (2). This is not surprising since, by Brown's account, the surgeon allowed the patient's beloved mastiff to remain in the operating theater during the surgery. Syme was opposed in his view by Dr. Joseph Lister (1827-1912) who believed that surgical extirpation of the disease represented the best hope of a cure (2). Moreover, he recognized that infection rather than breast cancer was responsible for the majority of surgical deaths (3). His epoch-making contribution of carbolic acid spray was not widely accepted for over 20 years after it was published. Syme and Lister argued about many issues in surgery and held each other in considerable contempt (it is worth noting that Syme's daughter Agnes, at the age of 24, married Joseph Lister).

At the turn of the century, William Stuart Halsted (1852-1922) from Johns Hopkins and Willie Meyer (1854-1932) from the New York Graduate School of Medicine described an operation–the radical mastectomy–that would remain the gold standard of care for nearly three quarters of the century (4). It is actually Meyer's operation that was popularized but Halsted's paper was published 10 days earlier (5). The Halstedian radical mastectomy reduced the local recurrence rate after surgery from 60% to less than 10% (6).

In 1948, two reports appeared that would change the management of the disease dramatically. That year, Patey and Dyson from the Middlesex Hospital in London described the modified radical mastectomy. Over the next 20 years, this operation grew in acceptance and popularity because it was effective as radical mastectomy yet much less debilitating (7). The same year, McWhirter, from Edinburgh, described the simple mastectomy with radiation therapy (8). Surgery was the sole treatment approach to breast cancer for over half of the 20th century, but the trend towards minimization of surgery supplemented by radiation therapy had begun.

In the 1950s, Jerome Urban, of Memorial Sloan-Kettering Cancer Center, Owen Wangensteen, and others advocated a 'supra-radical mastectomy' in which the dissection was carried into the mediastinum and often the neck (9). After much study, however, this technique was abandoned, having failed to improve survival rates.

By the 1960s, interest was growing in techniques that were able to conserve the breast. Guy's Hospital in London reported the earliest trial of breast conservation therapy (BCT), defined as tumorectomy, axillary dissection, and radiation therapy (10). The trials were prematurely terminated due to a high local recurrence rate, and this finding almost resulted in abandonment of BCT attempts (in hindsight, the radiation doses in this trial were clearly subtherapeutic). In the late 1960s, Professor Umberto Veronesi asked permission from the World Health Organization to include a breast conservation arm in a trial of radical mastectomy; he was immediately denied. The following year he was successful in including the BCT arm, and the treatment compared favorably with mastectomy. His subsequent Milan I and Milan II trials further demonstrated the safety of conserving the breast (11). At the same time, Dr. Bernard Fisher, who headed the National Surgical Adjuvant

Breast and Bowel Project (NSABP), commenced the B-06 trial which randomized women to mastectomy or lumpectomy with or without radiation therapy (12). This landmark trial confirmed the appropriateness of conserving the breast in selected patients. Following the B-06 and other trials, the National Cancer Institute issued a consensus statement which described BCT as equivalent to mastectomy yet preferable because it is less mutilating (13).

The next major surgical step towards the ideal therapy for breast cancer will likely be sentinel node mapping, a new technique that is rapidly gaining acceptance. It is based upon the proven hypothesis that there is a first node(s) that represents the most likely site of spread of breast cancer (14). If the true sentinel node is negative, it may be unnecessary to remove additional lymph nodes. At Memorial Sloan-Kettering, we have performed approximately 1600 sentinel node mapping procedures to date using a combination of blue dye (intraparenchymal) and 99Tc sulfur colloid tracer (intradermal). Patients with a successful mapping procedure and a negative node do not undergo further axillary surgery in our practice.

Chemotherapy

The use of chemical compounds, especially arsenic, in the treatment of breast cancer, dates to ancient times. In modern times, Paul Ehrlich (1854-1915) has been called the "Father of Chemotherapy." He is credited with coining the term and had isolated the first alkylating agent by 1898, though it was not until after World War II that his work was revived and applied to the treatment of tumors (15).

During WWII, a ship containing nitrogen mustard, a potent alkylating agent, exploded in Naples harbor. Sailors exposed to the compound developed marrow and lymphoid hypoplasia. This event led directly to experiments at Memorial Sloan-Kettering using similar agents in the treatment of lymphosarcoma (16). The results of these experiments were held confidential until after the war secrecy ban was lifted in 1946, and, soon after, analogues of these alkylating compounds, such as chlorambucil, cyclophosphamide, busulfan, and phenylalanine, appeared for clinical and experimental use. In 1957, Heidelberger and colleagues reported the action against solid tumors of 5-fluorouracil (17), which has remained popular in the treatment of breast cancer for half a century.

Over the last 3 decades, a large number of clinical trials using a broad spectrum of drugs demonstrated that survival could be increased in patients with operable breast cancer when systemic therapy was included. In the 1980s, the combination of cyclophosphamide, methotrexate, and 5-flourouracil (CMF) was the most popular combination of agents.

Today a significant majority of patients with invasive carcinomas measuring greater than 1 cm receives some form of adjuvant therapy. Doxorubicin has emerged as the most potent induction agent and has become a common component of adjuvant therapy for patients with positive axillary nodes. Recent information suggests that the status of the oncogene *HER2/neu* may be highly predictive of response to doxorubicin and may further select patients for this treatment. The discovery of a mitotic spindle-stabilizing agent called taxol has added another potent agent to the breast cancer armamentarium. Taxol has established itself as a potent cytotoxic agent against breast cancer, and there has been a recent trend towards giving doxorubicin and taxol to all patients with positive axillary nodes. There is also growing interest in using the doxorubicin/taxol combination of induction agents to facilitate BCT in patients with larger tumors.

The 1999 meeting of the American Society of Clinical Oncology highlighted the fact that very high-dose chemotherapy with bone marrow transplantation or stem cell support was not currently justified outside of the clinical trial setting (18). At the same meeting, Dr. Larry Norton reported that the combination of Herceptin plus taxol improves objective response rates and prolongs survival when compared with monotherapeutic cytotoxic strategies (19). There was also much interest in drugs that inhibit signal transduction pathways and cell cycle modulators.

Hormonal manipulations have also occupied a major place in the systemic therapy of breast cancer with agents such as tamoxifen. Tamoxifen, one of the most commonly prescribed anti-cancer agents in the world today, dramatically impacts the likelihood of systemic relapse in selected patient subsets. Today tamoxifen is being used not only as an adjunct in patients with invasive disease, but also as (putative) prevention in patients with noninvasive carcinoma and even in high-risk women who have never had breast cancer.

Future Directions

It is always risky to predict trends in medicine, but several directions seem inevitable. First and foremost, the trend from descriptive to molecular pathology will undoubtedly continue. Large families of breast cancers will come to be identifiable by their genetic footprint and the current staging system, which is lacking in so many ways, will wind up a footnote in future book chapters on breast cancer. Molecular staging will consider factors such as the magnitude of genome-wide instability/damage in tumors, aberrant signal transduction pathways, expression/mutation of key genes, and receptors. At the Memorial Sloan-Kettering Breast Cancer Research Laboratory, genotype/phenotype matching represents our largest area of study.

The trend towards surgical minimalism will continue, albeit with the premise that local control is vital, particularly as tumors are being diagnosed at earlier and earlier stages. Refinements in radiation therapy, including the type of groundbreaking work in brachytherapy that has been pioneered by Drs. Robert Kuske and John Bolton at the Ochsner Clinic (20), will expand and allow more patients to conserve their breasts. Sentinel node mapping will become entrenched in the mainstream, and hundreds of thousands of women in this country will be spared radical axillary surgery.

Systemic therapy will remain central to the treatment of invasive breast cancer, although strategies targeting specific abnormalities will lead to less toxic therapies. This could lead to an eventual phase-out of cytotoxic chemotherapy. Vaccine programs currently suffer from the lack of a unique breast cancer epitope/antigen, the discovery of which will revolutionize immunotherapeutic approaches. Agents such as Herceptin will continue to achieve long disease-free intervals in subsets of patients and when combined with conventional agents in patients with stage IV breast cancer will improve the cure rate of this uniformly fatal condition. Primary prevention will not find its foundation in prophylactic mastectomy but rather will result from combined medical approaches, for example, using a SERM administered with an aromatase inhibitor.

Genetic testing for susceptibility will expand as lower-penetrance genes that describe large subsets of breast cancers are identified. It may also become feasible to screen for mutation in the remaining allele of dominant tumor suppressor genes, thus facilitating not only risk assessment but also the prediction of the likely timing of cancer formation. The breast cancer advocacy community will have to remain vigilant for discrimination against these patients as it will become increasingly attractive to create "ghettos" of uninsurable women at greatly increased risk of breast cancer development.

Conclusions

Medical history will record that breast cancer was one of the most significant health threats facing women in the 20th century. In the 1990s alone, more American women died of the disease than all the U.S. lives lost in war from the Civil War to Vietnam. It has been (conservatively) estimated that 1,000,000 women died of breast cancer in this country between 1950 and 1990 (21). From 1930 to 1990 there was *NO* improvement in cure rates; however, in the mid-1990s a clear trend towards better survival was noted. There is every reason to be optimistic about the new millennium. Public awareness and involvement, philanthropic support, increased governmental awareness and funding of research, specialized training programs, all coupled with technologic advancements and clinical trials, will dramatically impact this disease and the lethal toll it has taken.

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